REMARKS

Claims 1-45, 47-58, and 60-71 are active in the present application. Claims 2, 5, 47 and 60 have been amended to incorporate Claims 46, 59 and 72. Claims 25 and 26 are amended to remove multiple dependencies. Claims 50, 51, 56, 64 are amended for clarity. No new matter is believed to have been added by these amendments.

Applicants wish to thank Examiner Fredman for the discussions held with the undersigned Applicants' representative on November 1 and 28, 2001. During these discussions, the undersigned asserted that the discovery of unique quenching rates of fluorescent dyes when coupled to the probes as claimed was not disclosed nor suggested in the cited prior art. The Examiner indicated that if the claims were amended to define a structural feature of the probe that was not present in the probes of the prior art references, he would reconsider the rejections set forth in the Office Action. Accordingly, Applicants point out that the amended independent claims have been amended to include specific dyes in the claimed probes, which probes are not disclosed in the art of record.

Favorable reconsideration and allowance of the claims is requested.

The rejection of Claims 2-7, 9, 46-48, 50 and 59 under 35 U.S.C. § 102(b) over Morrison et al (Anal. Biochem. (1989) 183:231-244) is respectfully traversed.

Morrison et al disclose probes labeled with fluorescein or pyrenebutyrate (Table 1).

However, Morrision et al do not disclose or suggest the claimed probes labeled with BODIPY FL, BODIPY FL/C3, 6-joe, BODIPY TMR, BODIPY FL/C6, Alexa 488, or Alexa 532.

Accordingly, the present claims are not anticipated by Morrison et al. Withdrawal of this ground of rejection is requested.

The rejection of Claims 2-7, 9, 46-48, 50 and 59 under 35 U.S.C. § 102(e) over Wittwer et al (US Patent 6,140,054) is respectfully traversed.

Wittwer et al disclose probes labeled with fluorescein or Cy5 (col. 21, lines 1-5).

However, Wittwer et al do not disclose or suggest the claimed probes labeled with BODIPY FL, BODIPY FL/C3, 6-joe, BODIPY TMR, BODIPY FL/C6, Alexa 488, or Alexa 532.

Accordingly, the present claims are not anticipated by Wittwer et al. Withdrawal of this ground of rejection is requested.

The rejection of Claims 2-11, 15, 46-53, 59-66 and 72 under 35 U.S.C. § 103(a) over Wittwer et al in view of Metelev et al is respectfully traversed.

As noted above, Wittwer et al disclose probes labeled with fluorescein or Cy5 (col. 21, lines 1-5). Metelev et al disclose oligonucleotide probes having a modified 2'O-methyl ribonucleotide, but does not disclose any of the dyes recited in the present claims.

Neither document suggests a probe labeled with BODIPY FL, BODIPY FL/C3, 6-joe, BODIPY TMR, BODIPY FL/C6, Alexa 488, or Alexa 532. Therefore, the present claims can not be obvious in view of the combination of Wittwer et al and Metelev et al.

Withdrawal of this ground of rejection is requested.

The rejection of Claims 2-9, 15, 21, 46-50, 53, 54, 59-63, 66, 67 and 72 under 35 U.S.C. § 103(a) over Wittwer et al in view of Hogan et al is respectfully traversed.

As noted above, Wittwer et al disclose probes labeled with fluoroscein or Cy5 (col. 21, lines 1-5). Hogan et al discloses employing helper probes to raise the T_m of hybrids with short probes and the target (see, for example, col.4, lines 44-50).

Neither document suggests a probe labeled with FITC, BODIPY FL, BODIPY FL/C3, 6-joe, BODIPY TMR, BODIPY FL/C6, Alexa 488, or Alexa 532. Therefore, the present claims can not be obvious in view of the combination of Wittwer et al and Hogan et al.

Withdrawal of this ground of rejection is requested.

The rejection of Claims 2-9, 15, 23, 24, 26, 46-50, 53, 55, 58-63, 66, 68, 69, 71 and 72 under 35 U.S.C. § 103(a) over Wittwer et al in view of Tyagi et al and further in view of Donovan et al is respectfully traversed.

As noted above, Wittwer et al disclose probes labeled with fluorescein or Cy5 (col. 21, lines 1-5). Tyagi et al disclose combinations of probes or combination of labeling moieties where one acts as a fluorophore and one acts as a quencher (see, for example, col. 3, lines 40-47). Tyagi et al discloses various dyes which can be used as fluorophores: including Fluorescein, Lucifer Yellow, and BODIPY (see col. 6).

Donnovan et al teach the use of fluorescent probes in nucleic acid arrays (col. 12, lines 44-67).

The Examiner contends that it would have been obvious to employ either the probes of Wittwer or Tyagi in the arrays of Donovan (page 7 of the Official Action). However,

Applicants submit that the combination of these three references still fail to make obvious the present claims where the probes have:

- at least one G (guanine) base exists in a base sequence of said target nucleic acid at a position 1 to 3 bases apart from an end base portion where said probe and said target nucleic acid are hybridized with each other labeled with specific dyes (see Claims 2 and 47); or
- a probe which has a base sequence designed such that, when said probe is hybridized with said target nucleic acid, base pairs in a probe-nucleic acid hybrid complex form at least one G (guanine) and C (cytosine) pair at said end portion labeled with specific dyes (see Claims 5 and 60);

Nothing in the cited references suggests combining these specific nucleotide configurations with the dyes recited in the present claims. Therefore, the combination of these documents do not support a *prima facie* case of obviousness.

In any case, even a *prima facie* case is rebutted by Applicants' showing already of record.

The inventors have "found that emission of fluorescence from a fluorescent dye decreases (quenching phenomenon of fluorescence) when a nucleic acid probe labeled with the fluorescent dye hybridizes to a target nucleic acid. . . [the inventors have] also found that the extent of this decrease varies depending on bases in a probe portion, to which the fluorescent dyes is conjugated, or on the sequence of bases" (page 2, line 18 to page 3, line 1 of the present specification).

The advantages of these probes are shown in the Examples section of the present application found on pages 65-108. In addition, Applicants have provided data in the form of an executed Declaration under 37 C.F.R. § 1.132 that demonstrates consistent quenching rates with BODIPY FL fluorescent dye when used in a hybridization experiment. These advantages were not suggested by the combined teachings of Wittwer, Tyagi and Donovan.

Withdrawal of this ground of rejection is requested.

The rejection of Claims 2-9, 15, 23-26, 46-50, 53, 55-63, 66, and 68-72 under 35 U.S.C. § 103(a) over Wittwer et al in view of Tyagi et al and further in view of Donovan et al and Heller et al is respectfully traversed.

The teachings and deficiencies of Wittwer et al, Tyagi et al and Donovan et al are discussed at length above. The addition of Heller et al to Wittwer et al, Tyagi et al and Donovan et al does not further strengthen a case of obviousness because, Heller et al merely teaches electronically controlling temperature as a means to control hybridization stringency.

Nothing in the cited references suggests combining the specific nucleotide configuration with the dyes recited in the present claims nor the advantages provide by this combination.

Accordingly, the present claims can not be obvious in view of Heller et al, Wittwer et al, Tyagi et al and Donovan et al and as such withdrawal of this ground of rejection is requested.

The rejection of Claims 50-52, 56-58 and 64-65 under 35 U.S.C. § 112, second paragraph is believed to be obviated by amendment.

The objection of Claims 25 and 26 under 37 C.F.R. 1.75(c) is believed to be obviated by amendment.

Applicants submit that the present application is now in a condition for allowance. Early notice of such allowance is earnestly solicited.

Respectfully submitted,

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IN THE CLAIMS

Please amend the claims as follows:

Please cancel Claims 46, 59 and 72.

2. (Amended) A nucleic acid probe for determining a concentration of a target nucleic acid, said probe being labeled with a fluorescent dye, wherein:

said probe is labeled at an end portion thereof with said fluorescent dye, and

said probe has a base sequence designed such that, when said probe is hybridized with said target nucleic acid, at least one G (guanine) base exists in a base sequence of said target nucleic acid at a position 1 to 3 bases apart from an end base portion where said probe and said target nucleic acid are hybridized with each other;

whereby said fluorescent dye is reduced in fluorescence emission when said probe is hybridized with said target nucleic acid, wherein said fluorescent dye is selected from the group consisting of BODIPY FL, BODIPY FL/C3, 6-joe, BODIPY TMR, BODIPY FL/C6, Alexa 488, and Alexa 532.

5. (Twice Amended) A nucleic acid probe for determining a concentration of a target nucleic acid, said probe being labeled with a fluorescent dye, wherein:

said probe is labeled at an end portion thereof with said fluorescent dye, and

said probe has a base sequence designed such that, when said probe is hybridized with said target nucleic acid, base pairs in a probe-nucleic acid hybrid complex form at least one G (guanine) and C (cytosine) pair at said end portion;

whereby said fluorescent dye is reduced in fluorescence emission when said probe is hybridized with said target nucleic acid, wherein said probe can be further extended at it's 3'-end by a DNA polymerase, wherein said fluorescent dye is selected from the group consisting of BODIPY FL, BODIPY FL/C3, 6-joe, BODIPY TMR, BODIPY FL/C6, Alexa 488, and Alexa 532.

25. (Twice Amended) The device according to claim 23 [or claim 24], wherein said probes or different probes bound on said surface of said solid support are each independently provided with at least one temperature sensor and at least one heater arranged on an opposite surface of said solid support such that an area of said solid support, where said probe or different probe is bound, can be controlled to meet optimal temperature conditions.

26. (Twice Amended) The device according to claim 23 [or claim 24], wherein said probe or different probes are bound at end portions, where said probes or different probes are labeled with no fluorescent dye on said surface of said solid support.

47. (Amended) A nucleic acid probe for determining a concentration of a target nucleic acid, said probe being labeled with a fluorescent dye, wherein:

said probe is labeled at an end portion thereof with said fluorescent dye, and

said probe has a base sequence designed such that, when said probe is hybridized with said target nucleic acid, base pairs in a probe-nucleic acid hybrid complex form at least one G (guanine) and C (cytosine) pair at said end portion;

whereby said fluorescent dye is reduced in fluorescence emission when said probe is hybridized with said target nucleic acid, wherein said probe has G or C as a 3' end base and is labeled at said 3' end thereof with said fluorescent dye, wherein said fluorescent dye is selected from the group consisting of BODIPY FL, BODIPY FL/C3, 6-joe, BODIPY TMR, BODIPY FL/C6, Alexa 488, and Alexa 532.

50. (Amended) The nucleic acid probe according to claim 47, [wherein an oligoribonucleotide of said probe is] which comprises a chemically-modified nucleic acid.

51. (Amended) The nucleic acid probe according to claim 47, wherein an oligonucleotide of said probe is a [chemiric] chimeric oligonucleotide comprising a ribonucleotide and a deoxyribonucleotide.

56. (Amended) The device according to claim 55, wherein said probes or said different [robes] probes are arranged and bound in an array pattern on said surface of said solid support.

60. (Amended) A nucleic acid probe for determining a concentration of a target nucleic acid, said probe being labeled with a fluorescent dye, wherein:

said probe is labeled at an end portion thereof with said fluorescent dye, and

said probe has a base sequence designed such that, when said probe is hybridized with said target nucleic acid, base pairs in a probe-nucleic acid hybrid complex form at least one G (guanine) and C (cytosine) pair at said end portion;

wherein said fluorescent dye is reduced in fluorescence emission when said probe is hybridized with said target nucleic acid, wherein said probe has C as a 5' end base and is labeled at said 5' end thereof with said fluorescent dye, and a hydroxyl group of a 2' or 3' carbon of a ribose, or a 3' carbon of a deoxyribose at the 3' end of said probe is

phosphorylated, wherein said fluorescent dye is selected from the group consisting of BODIPY FL, BODIPY FL/C3, 6-joe, BODIPY TMR, BODIPY FL/C6, Alexa 488, and Alexa 532.

64. (Amended) The nucleic acid probe according to claim 60, wherein an oligonucleotide of said probe is a [chemiric] chimeric oligonucleotide comprising a ribonucleotide and a deoxyribonucleotide.